REMARKS

The present application is directed to a method for detecting one or more biological entities in a sample and for obtaining information resident in the genetic code of a biological entity in a sample. The method is particularly useful for the detection or characterization of a pathogen, such as a biological weapon. Currently, Claims 16-63, 80-125, 127-130, 136-147 are pending in the application with Claims 1-15, 64-79, 126, and 131-135 canceled without prejudice to, or disclaimer of, the material claimed and new Claims 143-147 added.

The independent claims are amended to describe a method for detecting one or more biological entities in a sample, comprising the step of combining one or more nucleic acid sequences in a sample with multiple primers comprising randomized nucleotide sequences, the randomized sequences being sufficiently randomized such that substantially all of the nucleic acid sequences of a biological entity are represented among amplification products. Also, the independent claims are amended to describe that the array may comprise redundancies (Claims 1, 32 and 80), negative and positive controls (Claim 32), and/or predetermined nucleic acids having a known spatial arrangement on the array (Claim 48). Support for the amendments and newly submitted claims can be found in the specification. Accordingly, no new matter is added.

Support for the amendment to describe multiple primers comprising randomized nucleotide sequences, where the randomized sequences are sufficiently randomized such that substantially all of the nucleic acid sequences of a biological entity are represented among amplification products is described in the specification, for example, from page 7, line 11-15 (¶0014 of the published application). Support for the amendments describing the use of redundancies and positive and negative controls is found in the specification, for example, at page 10, lines 29-30 (¶0026), and support for an array comprising predetermined nucleic acids having a known spatial arrangement is found, for example, from page 6, line 29 to page 7, line 2 (¶0013).

Support for newly added Claim 143 is found, for example, on page 10, lines 29-31 (¶0026); support for newly added Claim 144 is found, for example, from page 10, line 31 to page 11, line 4 (¶0026); support for newly added Claims 145 and 146 is found, for example, on page

6, line 19 to 22 (¶0013); and support for newly added Claim 147 is found, for example, on page 7, lines 3-4 (¶0014).

Summary of Record of Interview

Applicants wish to thank the Examiner for the helpful suggestions made during an interview with one of the applicants, Paul Schaudies, and applicants' representative, Jamie Greene, on November 29, 2005. During the interview, proposed amendments to the claims to overcome the 35 U.S.C. § 112, first paragraph, rejection and proposed amendments to the claims to overcome the 35 U.S.C. § 103 rejection in view of the Beattie *et al.* and Peng *et al.* references were discussed. The insufficiencies of the Declaration Under 37 C.F.R. § 1.132, filed July 30, 2003, were also discussed, and the Examiner recommended that applicants file a Declaration Under 37 C.F.R. § 1.132 demonstrating unexpected results.

The Rejection Of The Claims Under 35 U.S.C. § 112, First Paragraph, Is Traversed Or Rendered Moot

In the Office Action mailed June 17, 2005, the Examiner rejected Claims 16-142 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement based on usage of the following terms: "nonpreferential start sites" (e.g., Claim 16); "nonpreferential length" (e.g., Claim 32); "an entirety of the nucleic acid sequences" (e.g., Claim 48); "even if identification of the biological entity cannot be ascertained" (Claim 104); "antibiotic" (Claim 107); "virulence" (Claim 108); "transmissibility" (Claim 109).

Applicants respectfully submit that support for the cited terms is inherent in the specification. However, to facilitate prosecution, and in no way acquiescing to the Examiner's basis for rejecting the claims, applicants have amended several of the claims to use terms that are more clearly described in the specification.

Applicants have amended the claims to remove the terms "nonpreferential start sites" and "nonpreferential length" and have replaced the term "substantially an entirety," with "substantially all" as suggested by the Examiner during the interview.

Regarding use of the language describing use of the assay to extract information about the biological entity, applicants have amended Claim 104 to remove the term "even if identity of the biological entity cannot be ascertained."

Applicants have replaced the word "antibiotic" in Claim 107 with the word "drug." This term has support in the specification as noted by the Examiner in the Office Action.

The Examiner stated that neither the term nor concept for "virulence" (Claim 108), or "transmissibility" (Claim 109) were described in the specification. Claim 108 has been amended to replace "virulence" with "identity of a pathogen," and Claim 109 has been amended to replace "transmissibility" with "spread of a communicable disease." Support for these amendments can be found in the specification on page 9, lines 23-31 (¶0021).

The Rejection Of The Claims Under 35 U.S.C. § 112, Second Paragraph, Is Traversed Or Rendered Moot

The Examiner stated that Claims 16-47, 80-137, and 139-142 were indefinite under 35 U.S.C. § 112, second paragraph, as indefinite for use of the language "nonpreferential" in relation to start sites or length. Applicants respectfully submit that this term is not in any way vague. However, to advance prosecution, applicants have amended the claims, as described above, to remove the term and respectfully request that the rejection be withdrawn.

The Rejection Of The Claims Under 35 U.S.C. § 103(a) Is Traversed Or Rendered Moot

A. Claims 16-23, 25-30, 32-39, 41-46, 48-55, 57-62, 64-71, 73-78, 80-87, 89-94, 96-112, 118, 119, and 121-141

The Examiner rejected Claims 16-23, 25-30, 32-39, 41-46, 48-55, 57-62, 64-71, 73-78, 80-87, 89-94, 96-112, 118, 119, and 121-141 under 35 U.S.C. § 103(a) as unpatentable over Beattie *et al.* (WO 97/22720) in view of Peng *et al.* (*J. Clin. Pathol.* (1994) 47:605-608) on the basis that Beattie teach the use of primers for PCR amplification of nucleic acids and hybridization of the amplified products to an array and Peng describe randomized primers. Applicants respectfully submit that the amendments to the claims overcome the rejection.

References fail to disclose elements of the claimed method

Applicants respectfully submit that the combination of Beattie and Peng fails to render the claims obvious under 35 U.S.C. § 103. Beattie describes hybridization of sample nucleic acid sequences to an array. However, where amplification of the sample nucleic acid sequences is utilized as part of the method, Beattie specifically teaches preparing amplified DNA that comprises a subset of the total nucleic acid sequences present in the sample. For example, Figure 1 of Beattie, showing a schematic overview of the assay, teaches that the amplified DNA comprises a subset of the genomic nucleic acid sequences. Also, in each and every description of nucleic acid amplification by PCR, Beattie describes that a subset of the original DNA sequences are amplified. See e.g., Beattie at pages 11, lines 9-15, page 19, lines 10-27, and pages 29-30, describing the use of primers that are 9-mers or greater in length for amplification of a subset of the starting DNA. Alternatively, Beattie describes the use of capture/hybridization probes to select for a subset of unamplified genomic DNA sequences for hybridization to an array. Thus, Beattie inherently relies on a two-step selection: (1) the use of specific primers for amplification of a subset of the DNA template, or capture of a subset of genomic DNA; and (2) measuring sequence-specific hybridization of the pre-selected subset.

Peng does not remedy the deficiencies of Beattie. Peng uses random primers to increase the amount of a DNA substrate prior to sequence-specific amplification of a subset of the nucleic acid sequences for further identification and/or characterization. Thus, Peng does not teach the direct characterization of nucleic acid sequences in the randomly amplified DNA, but requires a second step, whereby a subset of the DNA is amplified.

In contrast to Beattie and Peng, applicants teach the direct characterization of nucleic acid sequences in a randomly amplified pool of DNA. Applicants' method teaches the use of random primers such that randomly amplified DNA is generated resulting in amplification of substantially all of the nucleic acid sequences of the biological entity. The randomly amplified DNA is then directly analyzed by hybridization to the array, which contains a pattern of nucleic acid sequences or redundancies that provide a high level of confidence in the result. Neither Beattie nor Peng describe, teach, or suggest that a pool of randomly amplified DNA may be used

as a probe for an array of oligonucleotides that contains patterns or redundancies. Thus, Peng does not use the randomly amplified DNA for analysis, but first amplifies a subset of the DNA using sequence-specific PCR. Similarly, Beattie specifically teaches that prior to hybridization to an oligonucleotide array, a specific subset of the DNA is amplified. Thus, Beattie and Peng fail to describe, teach, or suggest each and every element of applicants' claimed method, either alone or in combination

No Motivation to Combine

Furthermore, even if the combination of the teachings of Beattie and Peng were to suggest applicants' method, which applicants do not concede, that there is absolutely no motivation to combine the methods of Beattie and Peng. Beattie is concerned with utilizing array hybridization rather than gel electrophoresis as a means to increase the speed and throughput for identification and characterization of amplification products. Thus, Beattie describes the use of primed PCR as a method to generate a subset of DNA molecules that may then be screened for sequence changes (e.g., polymorphisms) or other variations. By replacing gel electrophoresis with hybridization to an array, Beattie describes that the analysis of the increasing numbers of amplified DNA products is possible.

In contrast, Peng is not concerned with the rapid throughput screening of multiple sequences. Instead, Peng is concerned with generating increased amounts of starting material that may be used for subsequent analysis by standard PCR. See e.g., Peng, page 605, left column, lines 13-16. Peng is an amplification system for use in circumstances when sample size is extremely limited. To achieve amplification without introducing numerous copy errors, Peng uses a multistep system. In Phase I of the amplification, a reduced amount of polymerase is combined with the sample and modified amplification cycles performed. In Phase II of the amplification, an additional amount of polymerase and reagents are added to the amplification product of Phase I and standard amplification cycles are employed. The resulting amplified DNA is then subjected to conventional PCR using specific matched primer pairs. The PCR products obtained using the specific matched primer pairs are then analyzed using agarose gel

electrophoresis. Thus, Peng is not concerned with a high-throughput system, but a method to increase the amount of usable DNA template.

References teach away from each other

Applicants further assert that both Beattie and Peng teach away from applicants' method. Beattie describes that using primers having the optimal length of 8-10 base pairs for amplification of genomic DNA will typically yield 50-100 bands in an electrophoretic assay, or only 50,000-100,000 bases pairs of the total 3 billion bases in the human genome. Also, Peng describes that once the initial random-primed amplification has been used to generate additional substrate, sequence-specific PCR must be used to amplify a specific subset of the DNA for analysis and/or to identify specific sequences.

Claimed method achieves unexpected results

Even if the Peng and Beattie methods could be combined in some way, which applicants do not concede, applicants respectfully submit that the claimed detection method achieves unexpected results. As described in the enclosed Declaration by R. Paul Schaudies Under 37 C.F.R. §1.132, the amplification step in the claimed method allows for essentially an entire target genome of interest to be amplified. This, combined with hybridization of amplification products to an array of predetermined oligonucleotides that represent a pattern or multiple sites in the target genome, allows for the generation of multiple positive signals. This increased redundancy results in a dramatic increase in the confidence with which a particular biological entity is detected and decreases the generation of false positive and false negative results.

For at least the above reasons, applicants respectfully traverse the rejection.

B. Claims 24, 40, 56, 72, and 88

The Examiner rejected Claims 24, 40, 56, 72 and 88 under 35 U.S.C. § 103(a) as unpatentable over Beattie, in view of Peng, further in view of Cronin, and further in view of the Boehringer-Manheim catalog, 1998, pages 70-76. Thus, the Examiner stated that Beattie in view of Peng do not teach the use of digoxigenin, but that the Boehringer-Mannheim catalogue

teaches labeling of PCR products using digoxigenin. (Applicants note that the Examiner does not describe the basis for including Cronin in the rejection of these claims.)

As discussed above, applicants respectfully maintain that Beattie in view of Peng fails to describe, teach or suggest the subject matter of the independent claims from which Claims 24, 40, 56, 72 and 88 depend. Applicants further assert that the Boehringer-Mannheim catalogue, which teaches labeling of PCR products using digoxigenin, does not remedy the deficiencies of Beattie and Peng. Thus, applicants respectfully assert that the combination of all three references fails to yield a teaching that creates a case of *prima facie* obviousness of applicants' currently pending claims. Therefore, applicants respectfully request that the rejection be withdrawn.

C. Claims 31, 47, 63, 79, 95, 113-117, and 142

The Examiner rejected Claims 31, 47, 63, 79, 95, 113-117 and 142 under 35 U.S.C. § 103(a) as being unpatentable over Beattie, in view of Peng, further in view of Cronin. The Examiner stated that Beattie in view of Peng do not teach oligonucleotides longer than 30 nucleotides in length, specific hybridization conditions, or tiled or redundant arrays.

As discussed above, applicants respectfully maintain that Beattie in view of Peng fails to describe, teach or suggest the claims from which Claims 31, 47, 63, 79, 95, 113-117 and 142 depend. Applicants further assert that Cronin, which teaches arrays that employ immobilized oligonucleotides of greater than 30 nucleotides, does not remedy the deficiencies of Beattie and Peng. Thus, applicants respectfully assert that the combination of all three references fails to yield a teaching that creates a case of *prima facie* obviousness of applicants' currently pending claims. Therefore, applicants respectfully request that the rejection be withdrawn.

CONCLUSION

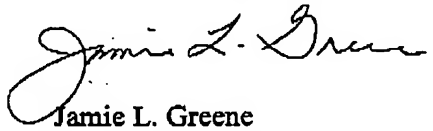
The foregoing is submitted as a full and complete Response to the Non-Final Office Action mailed on June 17, 2005. For at least the reasons given above, applicants respectfully submit that the pending claims comply with the written description requirement, are definite and

non-obvious. Accordingly, applicants submit that the claims are in condition for allowance, and such action is courteously solicited.

If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application that may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

No additional fees are believed due; however the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment to Deposit Account number 11-0855.

Respectfully submitted,



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